Phosphate concentration in ophthalmic corticoid preparations

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Abstract: BACKGROUND: Topical preparations, high in phosphate, may cause calcification when used on a damaged corneal surface. The knowledge of the phosphate concentration in medications helps to prevent corneal calcifications. Our study gives an overview of the amount of phosphate contained in ophthalmic corticoid preparations. METHODS: Samples of 38 commercially available corticoid preparations were tested. The quantification of phosphate was performed using the molybdate method on a Modular P autoanalyzer. RESULTS: 18 of 38 preparations (47%) had a phosphate concentration above physiological levels (>1.45 mmol/l). It varied greatly, and ranged from less than 0.1 mmol/l (18 preparations) to 62.6 mmol/l. The corticoids that were tested included betamethasone sodium phosphate (18.3-35.5 mmol/l), dexamethasone (0.1-17.6 mmol/l), dexamethasone sodium phosphate (<0.1-62.6 mmol/l), fluorometholone (<0.1-22.5 mmol/l), and prednisolone acetate (<0.1-0.5 mmol/l). CONCLUSIONS: The phosphate concentration in corticoid-phosphate formulations varies greatly, and is mainly determined by the chosen buffer. The prednisolone acetate preparations showed physiological phosphate concentrations. For a treatment on a damaged corneal surface, preparations with physiological phosphate concentrations should be used.

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BASIC SCIENCE

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Conclusions The phosphate concentration in corticoid-phosphate formulations varies greatly, and is mainly determined by the chosen buffer. The prednisolone acetate preparations showed physiological phosphate concentrations. For a treatment on a damaged corneal surface, preparations with physiological phosphate concentrations should be used.

Keywords Buffer · Cornea · Corneal calcification · Phosphate concentration · Steroids

Introduction

Eye-drop preparations, high in phosphate, may cause severe corneal calcification when used on a damaged ocular surface [1–4]. Daly et al. reported rapid corneal calcification in chemically injured eyes after irrigation with phosphate-buffered saline [2]. Similar irreversible deposits were described after ocular surface disease and frequent use of phosphate-buffered hyaluronic acid artificial tears [3], and after amniotic membrane transplantation with phosphate-rich lubrication [4].

Different corticoid compounds are presently used for the topical treatment of chemical burns, postoperative tissue injury, ocular surface disease and inflammatory conditions [5]. Affected eyes may develop corneal epithelial defects, and thus become susceptible to corneal calcification when exposed to phosphate-rich preparations.

There is only a small amount of information on the phosphate content of topical preparations [6] since buffers are regarded as additives. In preparations containing corticoid-

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Proprietary interest: none.

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Table 1 Phosphate concentration in commercially available preparations that contain corticoids (German and Swiss market)

Pharmacological agents	***Type of Corticoid***	***Phosphate PO4---*** *mmol/l*	***Market*** *Germany (GER) Switzerland (CH)*
Steroids			
Dexafree DU 0.1% (Théa Pharma)	*Dexamethasone sodium phosphate*	29.4	CH
DexaEDO (Mann)	*Dexamethasone sodium phosphate*	33.1	GER
Dexagel (Mann)	*Dexamethasone sodium phosphate*	<0.1	GER
Dexapos (Ursapharm)	*Dexamethasone sodium phosphate*	<0.1	GER
Dexa-sine SE (Alcon)	*Dexamethasone sodium phosphate*	48.1	GER
Efflumidex (Pharm-Allergan)	*Fluorometholone*	21.1	GER
Fluoro-Ophthal (Winzer)	*Fluorometholone*	12.7	GER
Fluoropos (Ursapharm)	*Fluorometholone*	11.7	GER
FML Liquifilm (Allergan)	*Fluorometholone*	22.5	CH
Inflanefran Forte (Pharm-Allergan)	*Prednisolone acetate*	<0.1	GER
Isopto-Dex (Alcon)	*Dexamethasone*	11.4	GER
Maxidex (Alcon)	*Dexamethasone*	17.6	CH
Predforte (Allergan)	*Prednisolone acetate*	0.5	CH
Predni-POS (Ursapharm)	*Prednisolone acetate*	<0.1	GER
Spersadex mono 0.1% (OmniVision)	*Dexamethasone sodium phosphate*	<0.1	GER, CH
Totocortin (Winzer)	*Dexamethasone sodium phosphate*	34.2	GER
Ultracortenol (Novartis Pharma)	*Prednisolone acetate*	<0.1	GER, CH
Vexol (Alcon)	*Rimexolone*	<0.1	GER, CH
Steroid combined with antibiotics			
Betagentam Augentropfen (Winzer)	*Betamethasone sodium phosphate*	18.3	GER
Cibaflam Augentropfensuspension (Novartis Pharma)	*Fluorometholone*	<0.1	GER
Dexa-Gentamicin (Ursapharm)	*Dexamethasone sodium phosphate*	52.6	GER
Dexamytrex -Augentropfen (Mann)	*Dexamethasone sodium phosphate*	62.6	GER
Dexa-Polyspectran (Alcon)	*Dexamethasone sodium phosphate*	2.8	GER
Dispadex comp. (OmniVision)	*Dexamethasone sodium phosphate*	<0.1	GER
FML-Neo Liquifilm (Allergan)	*Fluorometholone*	22.5	CH
Frakidex (Novartis Pharma)	*Dexamethasone sodium phosphate*	<0.1	CH
Infectoflam (Novartis Pharma)	*Fluorometholone*	<0.1	CH
Inflanegent Liquifilm (Pharm-Allergan)	*Prednisolone acetate*	<0.1	GER
Isopto-Max (Alcon)	*Dexamethasone*	<0.1	GER
Maxitrol (Alcon)	*Dexamethasone*	<0.1	GER, CH
Mycinopred (Allergan)	*Prednisolone acetate*	0.2	CH
Neo-Hydro Augentropfen (Streuli Pharma)	*Hydrocortisone acetate*	<0.1	CH
Ophtasone (Bausch & Lomb Switzerland)	*Betamethasone sodium phosphate*	35.5	CH
Terracortril N Betamethason + Gentamicin (Mann)	*Betamethasone sodium phosphate*	18.4	GER
Tobradex (Alcon)	*Dexamethasone*	<0.1	GER, CH
Steroid with chloamphenicol			
Aquapred-N (Winzer)	*Prednisolone sodium phosphate*	1.5	GER
Steroid and vasoconstrictor			
Efemoline (Novartis)	*Fluorometholone*	<0.1	GER, CH
Steroid and disinfection			
Dexa Biciron (Alcon)	*Dexamethasone isonicotinate*	<0.1	GER

phosphates, small amounts (<0.1 mmol/l) of free phosphate anions may be due to ester hydrolysis. Phosphorylated corticoids are popular with manufacturers, since they allow preparation of a clear solution [5].

Our study investigates the amount of phosphate contained in ophthalmic corticoid preparations. This information should help to prevent sight-threatening corneal calcification.

Materials and methods

All the ophthalmic drop preparations that contain corticoids and that are listed in the "Rote Liste 2007" (Rote Liste Service GmbH, Frankfurt/Main, Editio Cantor Verlag, Aulendorf, Germany) and the "Arzneimittelkompendium der Schweiz 2007" (Documed AG, Basel, Switzerland) were included in this study. When the preparations were available in multidose and unit dose containers, the samples were taken from the preservative-free formulation. For technical reasons, gel preparations were not included. The quantification of the phosphate was performed with the molybdate method on a Modular P autoanalyzer (Roche Diagnostics, Basel, Switzerland) [7]. The precision of these measurements was guaranteed by the inclusion of standardised phosphate solutions as controls. The day-to-day coefficient of variation was 1.7%. The results were compared to the physiological concentrations published elsewhere [7, 8].

Results

The phosphate concentrations of the ocular therapeutics that were studied are given in Table 1. The preparations are listed in alphabetical order and in groups of active drugs. The steroid compound of the therapeutic is shown in the second column.

Eighteen of 38 corticoid preparations (47%) had a phosphate concentration above physiological levels (>1.45 mmol/l). The concentration varied greatly and ranged from less than 0.1 to 62.6 mmol/l. Medications with betamethasone sodium phosphate showed phosphate concentrations from 18.3 to 35.5 mmol/l, dexamethasone from less than 0.1 to 17.6 mmol/l, dexamethasone sodium phosphate from <0.1 to 62.6 mmol/l, fluorometholone from <0.1 to 22.5 mmol/l, and prednisolone acetate from <0.1 to 0.5 mmol/l.

Discussion

Ophthalmic preparations with corticoids may contain high concentrations of free phosphate. Several medications with *phosphorylated* corticoids were, however, very low in free phosphate ion (Table 1). This indicates that in corticoid eye drops, as in other ophthalmic preparations [9, 10], the total amount of free phosphate ion is primarily determined by the choice of the buffers, and that phosphate ester bounds resist hydrolysis.

In ophthalmic preparations, the vehicle is an agent other than the active drug or preservative. It is added to a formulation to provide proper tonicity, buffering, and viscosity to complement drug action [11]. Its buffering system may consist of acetic, boric and hydrochloric acid, and of potassium or sodium bicarbonate, borate, phosphate and citrate [11]. Phosphates are presently widely used in ophthalmic preparations due to their high buffering capacity around pH 7.4.

Phosphate buffers, however, play a role in the process of inadvertent corneal calcification [1–4, 12]. Calcification occurs when calcium cations and phosphate anions interact within the tissue to form insoluble crystals. In the cornea, deposition typically occurs as hydroxylapatite $Ca_5(PO_4)_3OH$ [2, 3]. Deposition can be observed as a spectrum of clinical findings, ranging from subtle superficial changes to massive calcification of the entire cornea with visual loss.

"Boundary conditions" for the onset of corneal calcification, particularly a critical concentration of phosphate anions, cannot be defined at present. In an animal model, rapid corneal calcification developed after chemical injury, combined with a large epithelial defect, an alkaline pH, when the eyes were irrigated with Isogutt (Dr. Winzer Pharma GmbH, Germany) [1]. In this formulation, a phosphate concentration of 148 mol/l was measured [6].

The amount of phosphate ion delivered to the ocular surface by ophthalmic corticoid formulations may appear minor when compared to the treatment of chemical injuries or epithelial defects with artificial tears [3, 9]. It has to be borne in mind, however, that the ion product of calcium cations and phosphate anions in aqueous humour, tears and interstitial fluids is, even under physiological conditions, close to their solubility product. A minor increase of one of the components may therefore push this system towards precipitation. Furthermore, corticoids are often used in severely damaged eyes that are prone to the complication of calcification. The high phosphate concentration of some steroid preparations may therefore trigger the process of crystallisation. We do recommend that steroid preparations with physiological phosphate concentrations are used in order to reduce the risk of corneal calcification, particularly when frequent application is required.

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